JAMA Clinical Guidelines Synopsis

Management of Crohn Disease in Adults

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GUIDELINE TITLE Management of Crohn's Disease in Adults

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PRIOR VERSION April 2018

DEVELOPER AND FUNDING SOURCE American College of Gastroenterology (ACG)

TARGET POPULATION Adults with suspected and diagnosed Crohn disease (CD)

SELECTED RECOMMENDATIONS

- Fecal calprotectin (cutoff, >50-100 µg/g) helps differentiate inflammatory from noninflammatory colon disease, especially in patients with persistent diarrhea (strong recommendation; moderate level of evidence [LOE]).
- Routine endoscopic surveillance for colorectal cancer (CRC) in patients with Crohn colitis is recommended for early detection and improved CRC-free survival (strong recommendation; moderate LOE).
- Controlled ileal-release budesonide (9 mg/d) is recommended for induction of symptomatic remission in patients with mildly to moderately active ileocecal CD (strong recommendation; moderate LOE).
- Oral mesalamine is not recommended for induction or maintenance in patients with mildly to moderately active CD (strong recommendation; moderate LOE).

Summary of the Clinical Problem

Crohn disease is a chronic idiopathic gastrointestinal inflammatory disorder that can involve any part of the gastrointestinal tract, particularly the terminal ileum and proximal colon. Abdominal pain, diarrhea, and fatigue are common; extraintestinal manifestations (weight loss; joint, skin, hepatobiliary, and eye involvement) can occur.[1] Treatment efficacy is assessed by symptom relief and mucosal healing on endoscopy.[2] Without proper treatment, most patients have progressive inflammation and risk of complications such as strictures, fistulas, and abscesses.

Supplemental content

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The updated ACG guidelines provide evidence-based recommendations for diagnosis, disease monitoring, and medical and surgical management and encourage shared decision-making.[2]

Characteristics of the Guideline Source

The guideline committee was composed of gastroenterology experts (eTable in the Supplement). Recommendations were supported by systematic literature reviews. Evidence and strength of the recommendations were based on the GRADE system (LOE, risk-benefit ratio, and patient preference). The guideline contained 35 recommendations, of which 21 were strong (18 with moderate and 3 with low LOE).

Evidence Base

Crohn disease diagnosis requires compatible symptoms, endoscopic and radiologic findings, and chronic inflammation on intestinal mucosal biopsy. Fecal calprotectin, a protein released by neutrophils during intestinal inflammation, is an effective screening measure for patients with symptoms concerning for CD and helps monitor disease activity and identify flares. A meta-analysis of 10 diagnostic accuracy studies (2719 participants; normal fecal calprotectin level defined as <50 µg/g in 8 studies and <100 µg/g in 2 studies) reported that elevated fecal calprotectin levels differentiated inflammatory bowel disease (CD or ulcerative colitis) from functional gastrointestinal disorders of the colon at a threshold of 50 to 100 µg/g with a sensitivity of 88% (95% CI, 80%-93%) and a specificity of 72% (95% CI, 59%-82%).[3]

Patients with long-standing CD involving at least 30% of the colon are at increased risk of CRC, suggested by a large multicenter study of surveillance colonoscopies (>10 years; 6909 patients) reporting 3.9% incidence of low-grade dysplasia, 0.71% high-grade dysplasia, and 0.39% adenocarcinoma.[4] Colorectal cancer risk increases with disease duration, greater involvement, severity, prior dysplasia or stricture, and family history of CRC. A meta-analysis of 5 observational studies (7199 patients with inflammatory bowel disease) reported that patients under routine endoscopic surveillance had a lower rate of CRC vs patients without surveillance (1.8% vs 3.2%; odds ratio, 0.58; 95% CI, 0.42-0.80; $P < .001$).[5] Routine endoscopic surveillance is recommended every 2 to 3 years starting 8 years after diagnosis of CD.[5] Patients with primary sclerosing cholangitis and CD are at increased risk of CRC and should have yearly colonoscopy.[6]

Budesonide is an oral corticosteroid that acts locally in the distal ileum and proximal colon, resulting in fewer systemic effects than prednisone. A controlled ileal-release formulation (9 mg/d) is recommended for patients with mild to moderate CD involving the ileocecal region.[1] In a double-blind randomized clinical trial (RCT) of 258 patients, clinical remission (CD activity index ≤150) occurred by 8 weeks in 51% (95% CI, 39%-63%) of patients treated with 9 mg/d of budesonide vs 20% of those receiving placebo ($P < .001$).[7] However, a meta-analysis of 6 RCTs comparing budesonide with placebo at 3 months did not show a clear remission benefit (64% with budesonide vs 52% with placebo; risk ratio, 1.25; 95% CI, 1.00-1.58). Accordingly, the guideline recommends that budesonide, like other corticosteroids, should not be continued as maintenance therapy beyond approximately 3 months.

Oral mesalamine is not recommended for induction or maintenance of remission in patients with mild to moderately active CD. A meta-analysis (4 RCTs; 647 patients) reported no difference in effectiveness of oral mesalamine vs placebo in patients with active CD (relative risk of failure to achieve remission, 0.91; 95% CI, 0.77-1.06) or in achieving mucosal healing.[8]

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First-line treatment for moderate to severe CD includes biologic therapies (monoclonal antibodies) and oral small molecule drugs. Therapeutic options for CD have expanded considerably since the 2018 guidelines. Therapies available at that time included anti–tumor necrosis factor (TNF) medications such as infliximab and adalimumab, anti-integrin therapies (vedolizumab), and interleukin 12/interleukin 23 antagonists (ustekinumab). New biologic therapies include interleukin 23 inhibitors (risankizumab, guselkumab, and mirikizumab) and oral Janus kinase 1 inhibitors (upadacitinib). These biologics have shown efficacy in multiple RCTs and have strong recommendations for induction and maintenance of remission in moderate to severe CD. Although there are few comparative trials, a 2025 American Gastroenterological Association synthesis systematic review reported that among patients with inadequate response to or intolerance of a biologic therapy, moderate-certainty evidence supported use of adalimumab, risankizumab, and guselkumab over vedolizumab and ustekinumab.[9] Ultimately, selection of a specific agent is guided by individual disease characteristics; complications such as strictures, fistulas, or abscesses; patient preferences regarding oral, intravenous, or subcutaneous therapy; and insurance coverage.

In an open-label trial of 386 patients with newly diagnosed moderate to severe CD, initial treatment with infliximab plus an immunomodulator (azathioprine, mercaptopurine, or methotrexate) was associated with improved steroid-free and surgery-free remission at 1 year vs a step-up approach, in which patients first received systemic corticosteroids followed by biologic therapy, if needed (79% vs 15%; difference, 64%; 95% CI, 57%-72%; $P < .001$).[10] These findings support early initiation of biologic therapy for patients with moderate to severe CD.

For patients with severe symptoms of CD, prednisone is typically initiated at 40 mg/d to rapidly decrease inflammation. After symptom improvement (typically 1-2 weeks), prednisone should be tapered to decrease the risk of adverse effects and symptom recurrence, and ideally continued no longer than 3 months.

Potential Harms of Therapy

Prior to initiation of immunosuppressive and/or biologic therapy, patients should be screened for tuberculosis and hepatitis B virus due to risk of reactivation of these infections. Anti-TNF therapies are associated with increased risks of common respiratory, skin, and urinary infections, and less commonly with fungal and mycobacterial infections. Compared with anti-TNF therapies, newer antibody therapies (ustekinumab, vedolizumab, risankizumab, guselkumab, and mirikizumab) are associated with lower risk of opportunistic infections. Anti-TNF therapies are also associated with increased risk of melanoma and psoriasiform skin lesions. Upadacitinib has a US Food and Drug Administration black box warning about risk of venous thromboembolism, major adverse cardiac events, increased all-cause mortality, serious infections, and malignancies. However, this warning was informed by safety data from tofacitinib (another Janus kinase inhibitor) in older patients with rheumatoid arthritis and cardiovascular risk factors, and its applicability to patients with inflammatory bowel disease is uncertain.[2]

Systemic corticosteroids are associated with infection, accelerated bone loss, diabetes, weight gain, hypertension, and adrenal suppression. Thiopurines such as azathioprine and mercaptopurine, commonly used with anti-TNF therapies, increase risk of opportunistic infections, hepatoxicity, and bone marrow suppression; long-term use is associated with increased risk of lymphoma and nonmelanoma skin cancer, although absolute incidence rates are low.

Discussion

Crohn disease diagnosis and monitoring require integration of symptom assessment with objective measures using endoscopy, imaging, and histology. Objective monitoring allows for early identification of ongoing inflammation and complications, which informs timely treatment decisions and improves outcomes. Given rapidly evolving CD therapies, close coordination with a gastroenterologist is recommended to guide shared decision-making, therapy selection, and ongoing disease monitoring to optimize outcomes.

Areas in Need of Future Study

Currently, no validated biomarkers or clinical tools reliably predict individual response to specific therapies for CD, limiting personalization of treatment selection. Additionally, effective medical therapies for perianal and fibrotic stricturing disease associated with CD are needed. Future research should focus on improved risk stratification, prognostic and predictive biomarkers, and optimal sequencing and combination of therapies to guide treatment decisions in CD.

ARTICLE INFORMATION

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